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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,122	04/20/2006	Sudha Shenoy	067437-5020US	2631

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/543,122	SHENOY ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-18 and 20-35* is/are pending in the application.

4a) Of the above claim(s) *8-18 and 23-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,18 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,4-18 and 20-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 7/28/08 has been entered in full. Claims 1, 2, 4-7, 17 and 20-22 are amended. Claims 3 and 19 are canceled.

Claims 1, 2, 4-17, 18 and 20-35 are pending.

Claims 8-17 and 23-35 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 2, 4-7, 18 and 20-22 are under consideration, in so far as they read upon the previously elected species ((1) Label – fluorescent group; (2) Arrestin – beta-arrestin-2, subspecies EGFP-Barr2-Ub48, corresponding to SEQ ID NO: 6; and (3) GPCR – Class A GPCR, subspecies β2AR).

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (4/28/08).

The objection to the declaration at pg 3 is *withdrawn* in view of the new Declaration filed by Applicants on 8/27/08.

The objections to the specification at pg 3 are *withdrawn* in view of Applicants' amendments to the specification (¶ 1, 27, 28 and 59).

All objections and/or rejections of claims 3 and 19 are moot in view of Applicants' cancellation of these claims.

The objection to claim 6 at 4 is *withdrawn* in view of Applicants' amendments to the claim.

The rejection of claims 1-2, 4-6, 18 and 19-22 under 35 U.S.C. § 101 because the claim invention is directed to non-statutory subject matter is *withdrawn* in view of Applicants' amendments to the claims. Applicants have amended the claims to limit the claimed invention to an "arrestin chimera". The specification at ¶ 93 defines an "arrestin chimera" as "the expression product resulting from the chimeric expression of both arrestin and ubiquitin thus forming an arrestin ubiquitin or ubiquitin-arrestin chimera.

Thus, the claimed invention is limited to ubiquitin-arrestin fusions that are expressed as a chimeric protein, which is sufficient to distinguish the claimed invention from ubiquitinated arrestin that is produced naturally produced naturally in cells expressing the β_2-adrenergic receptor (β_2AR) when said cells are contacted with an agonist of the receptor (Shenoy et al, 2001; reference C24 on the 6/19/06 IDS).

The rejection of claim 7 under 35 U.S.C § 112, second paragraph, at pg 5 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claim.

The rejections of claims 1-2, 4-6, 18 and 19-22 under 35 U.S.C. § 102(b) as being anticipated by Shenoy et al (2001; reference C24 on the 6/19/06 IDS) is *withdrawn* in view of Applicants' amendments to the claims. The claim amendments distinguish the claimed invention from the ubiquitinated arrestin taught by Shenoy for the same reasons described above.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-7, 18 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an arrestin chimera comprising a naturally occurring beta-arrestin-2 and a naturally occurring ubiquitin moiety (including a an arrestin chimera comprising SEQ ID NO: 2), wherein the arrestin chimera has an increased affinity for a GPCR, as compared to the affinity of a wild-type arrestin, and wherein increased affinity means that the arrestin chimera remains associated with the GPCR and traffics with the GPCR into endosomes, and wherein the arrestin chimera does not dissociate at or near the plasma membrane,

does not reasonably provide enablement for an arrestin chimera comprising an arrestin or a fragment of arrestin and a ubiquitin moiety or a fragment of ubiquitin,

wherein the arrestin chimera has an increased affinity for a GPCR, as compared to the affinity of a wild-type arrestin, and wherein increased affinity means that the arrestin chimera remains associated with the GPCR and traffics with the GPCR into endosomes, and wherein the arrestin chimera does not dissociate at or near the plasma membrane. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The rejection is first restated in view of Applicants' amendments to the claims, and then Applicants' arguments are addressed.

The nature of the invention is an arrestin chimera comprising an arrestin and a ubiquitin molecule and with the recited functional characteristics (lines 3-6 of claim 1).

The scope of the claims is as follows. The specification teaches that the term "arrestin" encompasses both "naturally occurring" and "engineered variants" of different types of arrestin (visual arrestin, cone arrestin β-arrestin 1 and β-arrestin 2; the elected species of arrestin under consideration is β-arrestin 2). The specification explicitly states that "[b]oth the arrestin and the ubiquitin may include one or more additions, substitutions, mutations, or deletions of amino acid residues (¶19 of the published application). Furthermore, dependent claim 22 specifically recites that the arrestin can be a "naturally occurring" or "engineered variant" version of an arrestin, for example β-arrestin2. Furthermore, the modified arrestin of claim 1 "comprises" such fragments and thus tolerates one or more amino acid changes (including one or more additions, deletions and/or substitutions) anywhere in the sequence of arrestin or ubiquitin. Thus, the "structural" limitation of claim 1 only requires some small portion (as small as a few

amino acids) of arrestin or ubiquitin. Thus, structurally claim 1 encompasses a chimeric arrestin comprising a vast genus of "engineered variants" of β-arrestin2 and/or ubiquitin, each of which must be constructed and tested to see if they meet the recited functional limitations (lines 3-6, starting with "has an increased affinity..."). Claims 2, 4, 5, 18 and 21 limit the modified one to with characteristics of ubiquitinated β-arrestin. Claim 6 limits the modified arrestin to one further comprising a label. Claim 20 limits the reference GPCR (of the functional limitation) to a "class A GPCR").

In contrast to the scope of the claims, the specification provides limited working examples of a modified arrestin. On page 54, the specification describes a YFP-β-arrestin2-Ub chimeric protein that has increased affinity for the GPCR β2AR, as compared with non-chimeric β-arrestin2. The sequence of this fusion protein appears to be disclosed as SEQ ID NO: 2 and in Figure 2 (and designated 'EYFP-Barr2-Ub'). This chimeric protein consists 525 amino acids, of which presumably ~238 correspond to the YFP (yellow fluorescent protein), indicating that ~287 correspond to the β-arrestin2 and ubiquitin proteins. As ubiquitin consists of 76 amino acids, the β-arrestin2 is ~211 amino acids. Thus, engineered variants of β-arrestin2 and ubiquitin together include up to ~287 different amino acid sites that can be altered by mutation (substitution, deletion or addition). The claims place no limitation on the number of mutations that can be included in the claimed chimeric protein.

The specification further discloses two similar constructs designated EYFP-Barr2-Ub48 (SEQ ID NO:4, Figure 9) and EGFP-Barr2-Ub48 (SEQ ID NO: 6, Figure 10). The specification does not clearly describe the nature of these other constructs; however, they appear to have a mutation at Lysine-48 of the ubiquitin protein, which reduces the formation of multi-ubiquitin chains. However, no teachings are provided regarding the influence of this mutation on the affinity of the modified arrestin as compared with wild-type arrestin, which can form multi-ubiquitin chains. As polyubiquitination is part of the process which targets membrane proteins to the proteasome or vacuole for degradation, the skilled artisan could not predict whether permanently monoubiquitinated arrestin would have less, equal or greater affinity than transiently polyubiquitinated arrestin (as occurs with wild type arrestin), and thus these

two species belong to the vast genus of variants that would need to be tested prior to using the full scope of the claims.

Furthermore, Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the naturally occurring β-arrestin2 and ubiquitin proteins (e.g., as found in SEQ ID NO: 2) and variants of each. If a modified arrestin comprising variants of the naturally occurring β-arrestin2 and ubiquitin proteins (e.g., as found in SEQ ID NO: 2) is to have a structure and function similar to the naturally occurring β-arrestin2 and ubiquitin proteins (e.g., as found in SEQ ID NO: 2), then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function. Conversely, if a protein variant need not have a disclosed property; the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (1990; cited previously); Ngo (1995; cited previously)]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork (2000); Skolnick et al (2000); Doerks (1998); Smith and Zhang (1997); Brenner (1999); Bork et al (1996); each cited previously).

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicants' arguments (728/08; pg 9-11) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the term "modified arrestin" has been amended to recite "arrestin chimera" and that this term is "sufficiently enabled by the present specification" as they are "described throughout the specification, and multiple working examples describe assays utilizing such chimeras, as the Office Action itself notes on page 6" (pg 10). Applicants further argue that determining whether a "particular configuration of arrestin and ubiquitin displays the functional elements recited in claim 1" would not require undue experimentation. Applicants further argue that

"practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result" (pg 10). Applicants argue that the "Federal Circuit has found that such extensive experimentation is not undue", pointing to *Hybritech v. Monoclonal Antibodies* (1986). Applicants argue that SEQ ID NO: 4 and 6 are enabled because the assays in specification could be used to test these particular chimeras for functionality as recited in the claims. Applicants further argue that "the presence or absence of working examples is but one factor to be taken into consideration in determining whether the specification is enabling for the full scope of the claims" and that MPEP 2164.02 states that "the consideration is whether one skilled in the art would be expected to extrapolate the provided examples across the scope of the entire claim" (pg 10). Applicants argue that the description of the arrestin chimeras and their functional elements provided in the present specification would allow the skilled artisan to extrapolate across the entire scope of the claims.

Applicants' arguments have been fully considered and are found persuasive in part, but the rejection is maintained for the following the reasons.

Applicants' amendments that limits the claims to "arrestin chimeras" is acknowledged. The specification provides a working example of one such chimera with ubiquitin at the 3' end of β-arrestin (SEQ ID NO: 2), and which has the functionality recited in the claims (as shown in Examples). Wild type β-arrestin is ubiquitinated on one or more of sixteen lysine residues (Shenoy et al, 2001; reference C24 on the 6/19/06 IDS). Therefore, the additional fused ubiquitin provides the functionality as recited in the claims. The skilled artisan would predict that these two functional sequences, if placed in a different order (e.g. with the ubiquitin at the 5' end of the arrestin) would likely produce a functional chimera. Therefore, in view of the teachings of the specification with regard to arrestin chimeras, it would not require undue experimentation to make and test arrestin chimeras encompassing naturally occurring β-arrestin 2 (the elected species of arrestin under consideration) and naturally occurring ubiquitin. Thus, Applicants' argument that determining whether a "particular

configuration of arrestin and ubiquitin displays the functional elements recited in claim 1" would not require undue experimentation is found to be persuasive.

However, the rejection is maintained because the claims encompass an essentially unlimited genus of chimeras of arrestin and ubiquitin variants that must be made and tested to determine whether or not they meet the functional limitations recited in the claims, and this would require undue experimentation. This vast genus includes the sequences of SEQ ID NO: 4 and 6, which each contain a mutant ubiquitin unable to form ubiquitin chains (and thus of unpredictable functionality) and therefore these species are included in the rejection. It is acknowledged that the specification teaches assays for testing for functionality as recited in the claims. However, the essentially limitless size of the genus to be tested (no structural limitations are required by the claims) coupled with the lack of guidance (in the specification) and the lack predictability (as taught by the relevant art cited in the rejection) in which mutations in the arrestin and/or ubiquitin will impact the functionality of chimera, renders the experimentation undue.

With respect to *Hybritech v. Monoclonal Antibodies* (1986), the fact pattern of this case and of the instant rejection are significantly different, and the court decisions are not binding with regard to the instant rejections. With respect to enablement under 112, 1st paragraph, *Hybritech* concerned whether a method of producing antibodies using a hybridoma was enabled, which is a significantly differs from the mutated arrestin and ubiquitin proteins encompassed by the instant claims. Furthermore, nowhere does *Hybritech* appear to state that "extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result" is not undue. Instead, *Hybritech* states that "[e]nablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention ... is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive … and is determined as of the filing date of the patent application, which was August 4, 1980" The rejection in the instant case is in accord

with this; for the reasons set forth in the rejection the amount of experimentation is unduly extensive to practice the full scope of the claimed invention.

The Examiner does not dispute that "the presence or absence of working examples is but one factor to be taken into consideration in determining whether the specification is enabling for the full scope of the claims" or that "the consideration is whether one skilled in the art would be expected to extrapolate the provided examples across the scope of the entire claim" (pg 10). However, the rejection set forth previously and maintained herein considered both the existence of working examples and the level of predictability in the art as part of a *Wands*-type analysis that also included the nature of the invention, the state of the prior art, the relative skill of those in the art, the level of predictability in the art, the breadth of claims, the amount of direction or guidance by the inventor, and the quantity of experimentation needed to make or use the invention.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646